# Influence of Estrogen on Fat Metabolism in Totally Depancreatized Dogs

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by

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**CONTENT**



## I. INTRODUCTION

Development of serious diabetes mellitus after total pancreatectomy was pointed out by von MERING and MINKOWSKI in 1889[1]. Many studies followed this on pathophysiology after total pancreatectomy.

Concerning the abnormality of fat metabolism, particularly concerning the occurrence of fatty liver, FISHER and others[2)3)] did much work in 1924. Namely, it was considered that totally depancreatized dogs cannot survive for long, even if they are treated with insulin of appropriate dosis. In addition, the most outstanding finding at autopsy is wide spread fat infiltration and degeneration of the liver.

Later MACLEOD[4)] discovered that totally depancreatized dogs can survive for long, occurrence of fatty liver being favorably prevented, by adding raw pancreatic tissue in diet. On the other hand, HERSHEY and SOSKIN[5)] reported that fatty liver can be as well prevented by the administration of lecithin as the administration of raw pancreatic tissue, and this effect of lecithin was explained to be attributable to choline by BEST and others[6)]. CHAIKOFF and others asserted that occurrence of fatty liver can be prevented by administration of suitable dosis of extract of fresh pancreatic tissue[7)8)9)], methionine[10)11)], casein[12)], crystalline trypsin[13)] and the substance extracted from the raw pancreatic tissue by CHAIKOFF, DRAGSTEDT and others as well as by administration of insulin[10)14)15)]. DRAGSTEDT[16)17)] asserted that the raw pancreatic tissue is effective for prevention

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of occurrence of fatty liver not because of anti-fatty liver substance contained in or pancreatic enzymes, but because of existence of a new pancreatic hormone, and he named this 'lipocaic'[18)19)].

On the contrary to these assertions, AOKI[20)], and later OSHITANI[21)], YAMAMOTO[22)], KOSAKI[23)] and others reported that occurrence of fatty liver can be prevented by administration of suitable dosis of insulin alone after total pancreatectomy, even if above mentioned substances are not administered. Furthermore, HONJO[24)25)] reported from his clinical observations that fatty liver could not be observed when suitable dosis of insulin was administered at least in the cases without postoperative complications and those with well preserved appetite after total pancreatectomy, and fatty liver which develops in totally depancreatized dogs should be accepted to belong to alimentary fatty liver and its occurrence largely depends upon the control of diabetes mellitus, in addition.

Lately, NISHIKAWA[26)], in his experiments on the influence of total pancreatectomy on the genital organs, discovered that general condition was better in totally depancreatized dogs with administration of estrogen compared with those treated with insulin alone. Based on this finding, following experiments were carried out in the aim of clarifying the influence of estrogen on fat metabolism, administering estrogen of various dosis alone or with simultaneous administration of insulin.

## II. MATERIALS AND METHODS

1. Materials

Adult mongrel dogs of both sexes weighing from 6 to 13 kg were used. Pre- and postoperative feeding was maintained with rice, a small amount of wheat and well boiled fish, twice a day appropriately in amount.

2. Methods

i. Production of Totally Depancreatized Dogs

Animals were kept away from diet for 24 hours. The abdomen was opened with upper median incision under intravenous anesthesia with thiopenthal sodium of 10 to 20 mg/kg body weight. The pancreas was isolated from the duodenal wall with careful attention of preserving the pancreaticoduodenal artery and vein and totally removed. These totally depancreatized dogs were divided into following 4 groups.

a) Group without administration of drugs : After total pancreatectomy, neither insulin nor estrogen was administered.

b) Group of simple administration of insulin : After total pancreatectomy, from 1.5 to 2.0 units/kg body weight of N.P.H. insulin (Shimizu Pharm. Co. Ltd.) was administered before breakfast every morning.

c) Group of simple administration of estrogen : After total pancreatectomy, from 1,000 to 20,000 units/kg body weight of Ovahormone Benzoate (Teikoku-Zoki Co. Ltd.) was administered before breakfast every morning without administration of insulin.

d) Group of simultaneous administration of insulin and estrogen : After total pancreatectomy, from 1.0 to 2.0 units/kg body weight of insulin and from 200 to 10,000 units/kg body weight of above mentioned Ovahormone Benzoate was administered every-day, the latter as estrogen.

ii. Survival Time

Postoperative survival time was studied in the above mentioned 4 groups.

iii. Fluctuation of Body Weight

Body weight was measured in the early morning before feeding in each group.

iv. Determination of Blood Sugar Level

Blood sugar level was determined following the method of SOMOGYI-NELSON[27] in the fasting state in the early morning.

v. Determination of Serum Lipids

Serum was taken in the fasting state in the early morning. Total cholesterol and cholesterol of free type was determined following the modified method of ZAK-KILLIANI[28], and esterified cholesterol was calculated from the difference between these two. Total phospholipids was obtained 25 times' amplification of phosphorus in lipids as obtained by the method of FISKE-SUBBARAW[29]. Total fatty acid was determined following the method of STERN-SHAPIRO[30]. Neutral fat and total lipids were calculated from the formula of STAMLER[31][32]. Non-esterified fatty acid was determined following the modified method of DOLE[33][34].

vi. Determination of Liver Fat

Amount of liver fat at autopsy was determined following the method of VAN de KAMER[35].

vii. Histological Examinations

Section of the liver taken at autopsy was stained by hematoxylin-eosin or Sudan III[36] for histrogical studies.

viii. Determination of Activity of Lipoprotein Lipase

Activity of lipoprotein lipase in blood was determined following the modified method of KORN[37][38].

As the substrate in this method, Fatgen (Dainihon Pharm, Co. Ltd.) was used, and 10 per cent solution of Fatgen of 20 cc/kg body weight was intravenously injected for determination of change of total fatty acid in blood.

## III. RESULTS

1. Survival Time after Total Pancreatectomy

Survival time after total pancreatectomy in group without administration of drugs is represented in Table 1, ranging from 6 to 14 days, about 10 days on the average.

**Table 1.** Suvival Time in Group without Administration of Drugs.

| Dog No. | Sex | Survival Time (Day) | Dosis of Insulin (u./kg) | Dosis of Estrogen (u./kg) |
|---|---|---|---|---|
| No. 1 | ♀ | 14 | — | — |
| No. 2 | ♂ | 6 | — | — |
| No. 3 | ♀ | 12 | — | — |
| No. 4 | ♂ | 11 | — | — |
| No. 5 | ♀ | 9 | — | — |
| No. 6 | ♂ | 7 | — | — |

**Table 2.** Survival Time in Group of Insulin Administration

| Dog No. | Sex | Survival Time (Day) | Dosis of Insulin (u./kg) | Dosis of Estrogen (u./kg) |
|---|---|---|---|---|
| No. 2 | ♂ | 46 | 1.5 | — |
| No. 3 | ♀ | 40 | 1.5 | — |
| No. 4 | ♂ | 31 | 1.5 | — |
| No. 5 | ♀ | 28 | 2.0 | — |

Survival time after total pancreatectomy in group of simple administration of insulin was 28 to 46 days, 36 days on the average, as shown in Table 2.

Survival time after total pancreatectomy in group of simple administration of estrogen was 4 to 107 days, a little more than 28 days on the average, as in Table 3.

In group of simultaneous administration of insulin and estrogen, survival time after total pancreatectomy was 18 to 131 days, a little more than 51 days on the average, as represented in Table 4.

**Table 3.** Survival Time in Group of Estrogen Administration

| Dog No. | Sex | Survival Time (day) | Dosis of Insulin (u./kg) | Dosis of Estrogen (u./kg) |
|---|---|---|---|---|
| No. 1 | 우 | 24 | — | 10,000 |
| No. 2 | 우 | 7 | — | 20,000 |
| No. 3 | 우 | 26 | — | 10,000 |
| No. 4 | 숫 | 4 | — | 20,000 |
| No. 5 | 숫 | 12 | — | 5,000 |
| No. 6 | 우 | 21 | — | 5,000 |
| No. 7 | 우 | 23 | — | 5,000 |
| No. 8 | 숫 | 18 | — | 4,000 |
| No. 9 | 숫 | 107 | — | 1,000 |
| No. 10 | 숫 | 30 | — | 1,000 |
| No. 11 | 숫 | 27 | — | 1,000 |
| No. 12 | 숫 | 35 | — | 1,000 |
| No. 13 | 우 | 28 | — | 1,000 |
| No. 14 | 우 | 29 | — | 1,000 |
| No. 15 | 우 | 45 | — | 1,000 |
| No. 16 | 우 | 19 | — | 1,000 |

**Table 4.** Survival Time of Group of Simultaneous Administration of Insulin and Estrogen.

| Dog No. | Sex | Survival Time (day) | Dosis of Insulin (u./kg) | Dosis of Estrogen (u./kg) |
|---|---|---|---|---|
| No. 1 | 숫 | 18 | 1.0 | 10,000 |
| No. 2 | 숫 | 50 | 2.0 | 1,000 |
| No. 3 | 숫 | 131 | 1.0 | 1,000 |
| No. 4 | 숫 | 23 | 1.0 | 1,000 |
| No. 5 | 우 | 18 | 2.0-0.5 | 1,000 |
| No. 6 | 숫 | 49 | 2.0 | 1,000 |
| No. 7 | 우 | 63 | 1.0 | 1,000 |
| No. 8 | 우 | 29 | 1.0 | 1,000 |
| No. 9 | 숫 | 37 | 2.0 | 1,000 |
| No. 10 | 우 | 53 | 1.0 | 1,000 |
| No. 11 | 숫 | 98 | 1.0 | 1,000 |

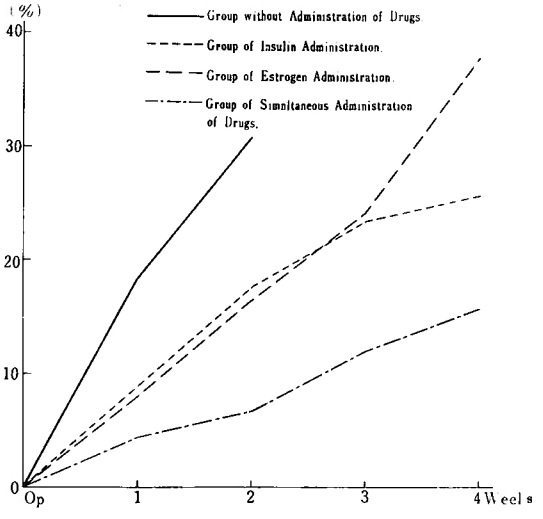
2. Fluctuation of Body Weight after Total Pancreatectomy

Rate of weight loss after total pancreatectomy is represented in Table 5 and Figure 1. Weight loss rate in group without administration was 18.3 per cent 1 week after surgery and 30.1 per cent 2 weeks after surgery. In group of simple administration of

**Table 5** Rate of Weight Loss. (Min—Max) (Mean)

| Group (No. of Dogs) \ after Surgery (Week) | 1 Week (%) | 2 Weeks (%) | 3 Weeks (%) | 4 Weeks (%) |
|---|---|---|---|---|
| Group without Administration of Drugs (5) | 14.3—18.8 (18.3) | 28.6—31.3 (30.1) | — | — |
| Group of Insulin Administration (4) | 4.9—12.5 (9.5) | 11.8—21.1 (17.4) | 16.0—29.2 (23.1) | 23.5—33.7 (25.5) |
| Group of Estrogen Administration (10) | 4.8—13.8 (9.3) | 6.7—31.0 (17.0) | 13.6—35.7 (23.6) | 36.8—39.3 (37.9) |
| Group of Simultaneous Administration of Insulin and Estrogen (6) | 0— 6.7 (4.4) | 5.6— 8.0 (6.2) | 5.6—25.0 (12.1) | 8.0—25.0 (15.7) |

**Fig. 1.** Rate of Weight Loss




insulin, the rate was 9.5 per cent 1 week after surgery, 17.4 per cent 2 weeks after surgery, 23.1 per cent 3 weeks after surgery and 25.5 per cent 4 weeks after surgery. In group of simple administration of estrogen, the rate was 9.3 per cent 1 week after surgery, 17.0 per cent 2 weeks after surgery, 23.6 per cent 3 weeks after surgery and 37.9 per cent 4 weeks after surgery. In group of simultaneous administration of insulin and estrogen, the rate was 4.4 per cent 1 week after surgery, 6.2 per cent 2 weeks after surgery, 12.1 per cent 3 weeks after surgery and 15.7 per cent 4 weeks after surgery.

3. Change in blood Suger Level after Total Pancreatectomy

Blood sugar level in each group showed the level of about 300 mg/dl after total pancreatectomy, with little difference from each other. (Table 6, Figure 2.)

**Table 6.** Change in Blood Sugar Level. (mg/dl)

| Group (No. of Dogs) \ Time after Surgery | 4 Days | 1 Week | 10 Days | 2 Weeks | 3 Weeks | 4 Weeks | 5 Weeks |
|---|---|---|---|---|---|---|---|
| Group without Administration of Drugs (4) | 323 | 346 | 369 | 402 | — | — | — |
| Group of Insulin Administration (4) | 284 | 298 | 306 | 346 | 327 | 317 | 309 |
| Group of Estrogen Administration (7) | 311 | 306 | 287 | 272 | 298 | 326 | 301 |
| Group of Simultaneous Administration of Insulin and Estrogen (5) | 268 | 329 | 292 | 264 | 283 | 315 | 303 |

4. Change in Serum Lipids after Total Pancreatectomy

i. Level of Serum Lipids Fraction in Normal Dogs.

As shown in Table 7, Serum lipids fraction was determined in the fasting state in the early morning in 14 normal dogs. Total cholesterol was 139.5mg/dl, esterified cholesterol 98.9 mg/dl, total phospholipids 151.3 mg/dl, total fatty acid 239.8 mg/dl, neutral fat 67.7 mg/dl, total lipids 421.8 mg/dl, cholesterol ester ratio 71.1 per cent, T.P./T.C. 1.09 and non-esterified fatty acid 558.2 $\mu$Eq/L, all on the average.

ii. Change in Serum Lipids Fraction after Total Pancreatectomy

Level of serum lipids fraction after total pancreatectomy is shown in Table 8, 9, 10 and 11.

Total cholesterol showed the tendency of increase as early as 4 days after surgery

**Fig. 2.** Change in Blood Sugar Level

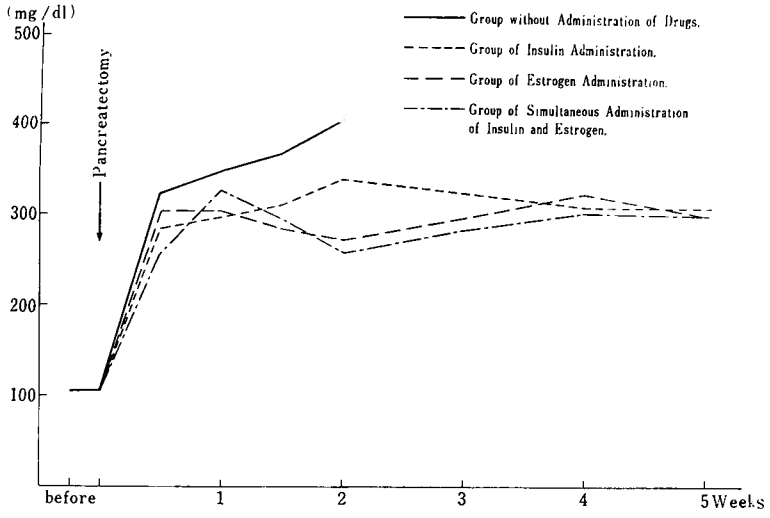



**Table 7.** Normal Level of Each Fraction of Lipids in Blood.

| Dog No. | Body Weight (kg) | Sex | T. C (mg/dl) | E. C (mg/dl) | T. P. L (mg/dl) | T. F. A (mg/dl) | N. F (mg/dl) | T. L (mg/dl) | E. R (%) | TP/TC | N.E.F.A.(μEq/l) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 6.0 | ♂ | 130 | 90 | 124.5 | 216.2 | 58.7 | 376.1 | 69.2 | 0.96 | 511 |
| 2 | 14.0 | ♂ | 140 | 119 | 175.0 | 238.6 | 36.1 | 436.3 | 85.0 | 1.25 | 549 |
| 3 | 9.5 | ♀ | 120 | 90 | 148.5 | 216.2 | 53.6 | 385.2 | 75.0 | 1.24 | 648 |
| 4 | 7.0 | ♂ | 154 | 88 | 178.6 | 267.5 | 87.7 | 480.4 | 57.1 | 1.16 | 676 |
| 5 | 6.0 | ♀ | 140 | 98 | 198.0 | 216.2 | 12.6 | 421.5 | 70.0 | 1.41 | 657 |
| 6 | 9.5 | ♀ | 180 | 130 | 202.5 | 260.2 | 31.4 | 407.3 | 72.2 | 1.13 | 505 |
| 7 | 11.0 | ♀ | 90 | 72 | 92.3 | 188.5 | 77.8 | 209.0 | 80.0 | 1.03 | 441 |
| 8 | 8.0 | ♂ | 116 | 78 | 165.0 | 288.3 | 126.8 | 458.7 | 67.2 | 1.42 | 670 |
| 9 | 10.5 | ♀ | 138 | 89 | 151.5 | 216.2 | 52.3 | 404.2 | 64.5 | 1.09 | 523 |
| 10 | 8.0 | ♂ | 152 | 114 | 141.0 | 271.7 | 98.7 | 480.2 | 75.0 | 0.93 | 523 |
| 11 | 8.0 | ♂ | 136 | 97 | 157.7 | 238.0 | 63.6 | 405.9 | 71.5 | 1.16 | 421 |
| 12 | 10.0 | ♀ | 125 | 87 | 102.8 | 255.0 | 116.1 | 401.9 | 70.0 | 0.82 | 678 |
| 13 | 12.0 | ♀ | 154 | 88 | 178.6 | 267.5 | 87.7 | 479.8 | 57.0 | 1.16 | 552 |
| 14 | 8.0 | ♂ | 175 | 143 | 108.8 | 216.2 | 40.8 | 427.1 | 81.7 | 0.62 | 461 |
| Mean | | | 139.5±24.6 | 98.9±22.7 | 151.3±35.9 | 239.8±29.7 | 67.7±33.8 | 421.8±41.4 | 71.1±8.5 | 1.09±0.22 | 558.2±87.5 |

*T.C. : Total Cholesterol. E. C. : Ester Cholesterol. T. P. L. : Total Phospholipids. T. F. A. : Total Fatty Acid. N. F. : Neutal Fat. T. L. : Total Lipids. E. R. : Cholesterol Ester Ratio. N. E. F. A. . Non-esterified Fatty Acid.

**Table 8.** Lipid Fraction in Dogs without Administration of Drugs (Mean Value of 4 Dogs ; No. 1, 3, 4, 5)

| | T. C (mg/dl) | E. C (mg/dl) | T. P. L (mg/dl) | T. F. A (mg/dl) | N. F (mg/dl) | T. L (mg/dl) | E. R (%) | TP/TC |
|---|---|---|---|---|---|---|---|---|
| before | 121.6±24.6 | 79.5±22.6 | 147.1± 39.1 | 251.7± 31.8 | 81.9±29.9 | 439.1± 57.1 | 70.9±8.6 | 1.02±0.21 |
| 4 Days | 315.0±88.0 | 202.5±50.5 | 304.5±103.5 | 551.6±169.1 | 209.4±69.5 | 1023.1±338.2 | 61.9±2.1 | 0.95±0.06 |
| 1 Week | 490.0±69.8 | 361.0±42.1 | 431.3± 96.6 | 804.2±111.1 | 264.3±73.8 | 1436.5±291.0 | 73.7±2.1 | 0.88±0.16 |
| 10 Days | 498.0±54.6 | 259.0±31.6 | 328.4± 97.0 | 868.5± 98.8 | 482.3±98.1 | 1474.9±341.7 | 52.0±1.9 | 0.66±0.29 |
| 12 Days | 574.0±31.8 | 248.0±28.9 | 337.5± 88.7 | 1053.4±131.8 | 537.9±77.7 | 1670.8±296.7 | 43.2±1.7 | 0.55±0.18 |

**Table 9.** Lipid Fraciton in Dogs of Insulin Administration.
(Mean Value of 4 Dogs ; No. 2, 3, 6, 8.)

| | T. C (mg/dl) | E. C (mg/dl) | T. P. L (mg/dl) | T. F. A (mg/dl) | N. F (mg/dl) | T. L (mg/dl) | E. R (%) | TP/TC |
|---|---|---|---|---|---|---|---|---|
| before | 110.0±26.3 | 78.0±17.3 | 120.0±21.1 | 243.9± 57.6 | 119.9±97.6 | 393.5±131.8 | 70.9±4.6 | 1.09±0.16 |
| 4 Days | 193.3±50.1 | 125.3±25.5 | 197.9±44.3 | 404.7± 48.0 | 191.7± 4.7 | 640.8±109.4 | 71.1±6.2 | 1.18±0.12 |
| 1 Week | 189.0±58.5 | 131.7±34.6 | 178.8±37.0 | 380.7±110.9 | 172.9±73.1 | 621.9±167.8 | 70.4±3.4 | 0.99±0.29 |
| 10 Days | 125.0±50.7 | 68.0±27.7 | 114.0±66.6 | 370.6± 57.9 | 256.8±48.9 | 533.2±111.2 | 54.4±3.3 | 0.91±0.31 |
| 2 Weeks | 169.5±63.5 | 111.0±40.0 | 144.0±68.0 | 421.3± 88.6 | 276.0±28.0 | 656.9±190.0 | 66.9±0.1 | 0.81±0.10 |
| 3 Weeks | 154.5±47.6 | 111.0±28.1 | 138.7±21.9 | 385.4± 33.3 | 198.6±37.8 | 585.6±181.7 | 71.2±2.8 | 0.89±0.18 |
| 4 Weeks | 176.5±26.4 | 117.5±30.3 | 168.0±37.3 | 395.0±116.1 | 156.0±97.5 | 576.9±169.4 | 65.5±4.5 | 0.95±0.19 |
| 5 Weeks | 121.5±27.3 | 74.0±24.7 | 101.6±26.2 | 318.8± 63.2 | 197.6±83.1 | 476.3± 88.8 | 52.7±5.3 | 0.98±0.10 |

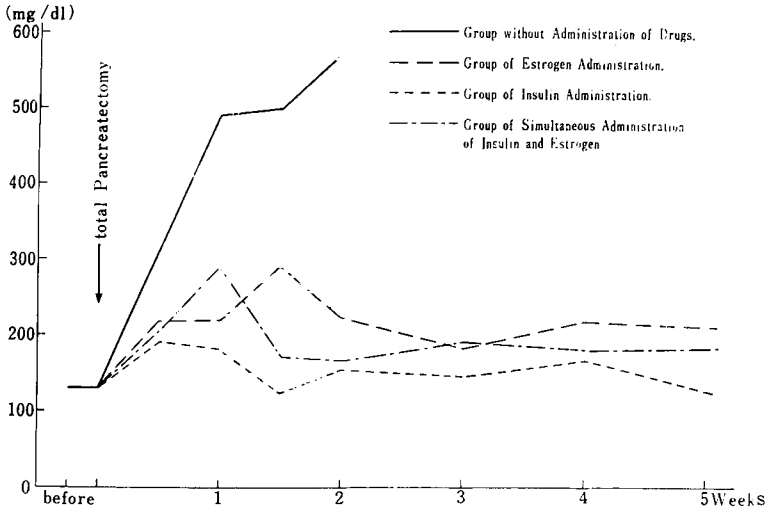
**Table 10.** Lipid Fraction in Dogs of Estrogen Administration.
(Mean Value of 7 Dogs : No. 9, 10, 11, 12, 13, 14, 15.)

| | T. C (mg/dl) | E. C (mg/dl) | T. P. L (mg/dl) | T. F. A (mg/dl) | N. F (mg/dl) | T. L (mg/dl) | E. R (%) | TP/TC |
|---|---|---|---|---|---|---|---|---|
| before | 128.0±23.4 | 111.0±24.7 | 137.5±19.7 | 229.9± 52.1 | 59.6± 27.8 | 403.0± 69.9 | 86.7±4.0 | 1.07±0.18 |
| 4 Days | 211.8±38.2 | 139.3±35.9 | 188.5±98.0 | 318.2± 80.4 | 174.3± 69.1 | 655.1±129.8 | 65.8±6.5 | 0.78±0.32 |
| 1 Week | 219.5±36.9 | 151.3±32.4 | 190.2±27.4 | 448.6± 51.2 | 196.4± 81.0 | 730.9± 80.6 | 68.5±3.6 | 0.89±0.23 |
| 10 Days | 292.0±18.7 | 204.0±28.6 | 249.8±47.8 | 498.2± 67.9 | 191.0± 61.7 | 891.1±102.0 | 69.9±4.7 | 0.86±0.18 |
| 2 Weeks | 222.5±20.6 | 153.8±31.2 | 202.0±57.1 | 446.5±137.7 | 208.9±119.1 | 735.4±154.8 | 68.6±9.7 | 0.91±0.24 |
| 3 Weeks | 181.0±16.0 | 142.5±19.5 | 131.3±15.6 | 371.5± 38.7 | 188.5± 14.6 | 595.8± 59.0 | 78.4±3.8 | 0.73±0.02 |
| 4 Weeks | 218.5±23.5 | 165.0±19.8 | 197.7±28.1 | 416.0± 74.7 | 171.2± 62.2 | 711.7± 91.3 | 75.0±6.8 | 0.90±0.11 |
| 5 Weeks | 213.7±11.0 | 143.0±12.3 | 211.9± 9.8 | 408.5± 21.7 | 170.2± 31.8 | 729.7± 87.3 | 66.9±2.3 | 0.99±0.09 |

**Table 11.** Lipid Fraction in Dogs of Simultaneous Administration of Insulin and Estrogen.
(Mean Value of 5 Dogs ; No. 2, 3, 7, 10, 11.)

| | T. C (mg/dl) | E. C (mg/dl) | T. P. L (mg/dl) | T. F. A (mg/dl) | N. F (mg/dl) | T. L (mg/dl) | E. R (%) | TP/TC |
|---|---|---|---|---|---|---|---|---|
| before | 157.0±24.6 | 111.0±18.5 | 185.2±24.6 | 255.5± 27.6 | 52.9± 28.7 | 473.6± 51.8 | 70.7± 8.6 | 1.18±0.17 |
| 4 Days | 208.0± 8.4 | 145.0±32.5 | 185.7±73.1 | 404.7± 11.1 | 177.0± 81.8 | 674.0± 9.1 | 64.9± 9.1 | 0.89±0.31 |
| 1 Week | 290.3±21.9 | 187.7±15.5 | 247.5±56.6 | 431.0± 60.0 | 134.7± 69.8 | 741.7±141.8 | 68.9± 5.4 | 0.90±0.18 |
| 10 Days | 178.0±31.1 | 130.0±33.7 | 218.0±57.5 | 264.7± 28.6 | 29,9± 58.8 | 519.4± 99.0 | 73.8± 4.7 | 1.21±0.01 |
| 2 Weeks | 169.3±48.6 | 127.3±48.0 | 169.3±65.6 | 340.0±131.5 | 140.4± 77.6 | 565.3±187.7 | 75.3± 1.0 | 1.03±0.22 |
| 3 Weeks | 195.7±65.3 | 140.3±52.4 | 199.8±17.7 | 382.5±122.6 | 153.5± 78.4 | 644.1±192.6 | 77.6±11.6 | 1.09±0.63 |
| 4 Weeks | 181.0±71.0 | 115.8±14.0 | 115.9± 7.9 | 312.8± 19.4 | 157.1± 30.7 | 524.2± 98.0 | 64.0±15.1 | 0.64±0.11 |
| 5 Weeks | 182.6±73.0 | 137.7±72.5 | 173.3±58.5 | 321.4± 16.6 | 110.0±109.7 | 576.8± 80.0 | 75.4± 6.6 | 0.95±0.04 |
| 6 Weeks | 206.4±91.5 | 165.0±72.6 | 187.8±38.8 | 358.8± 97.5 | 118.1± 28.9 | 632.5± 87.6 | 79.9±16.1 | 0.91±0.15 |

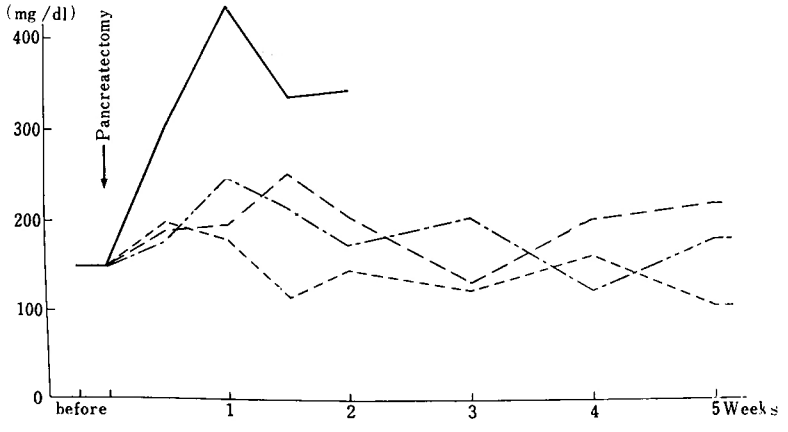
**Fig 3.** Change in Total Cholesterol




in all groups as shown in Figure 3, with little difference from each other in groups of simple administration of either insulin or estrogen and of simultaneous administration of these both. The level had its peak around 10 days after surgery, restoring to normal from 3 to 4 weeks after surgery. However, in group without administration of drugs, total cholesterol increased on showing as high a level as 574 mg/dl immediately before death.

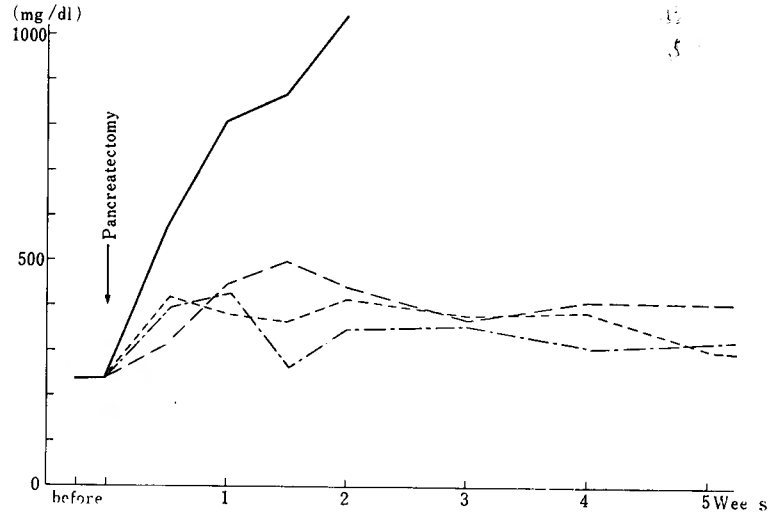
Total phospholipids slightly fluctuated without definite tendency after surgery in groups of simple administration of either insulin or estrogen and of simultaneous administration of these two, as shown in Figure 4. In group without administration of drugs, total phospholipids showed considerably high level compared with other groups, being 431.3 mg/dl 1 week after surgery. However, it slightly decreased 10 or 14 days after surgery, although maintained in a higher level than in other 3 groups.

**Fig. 4.** Change in Total Phospholipids



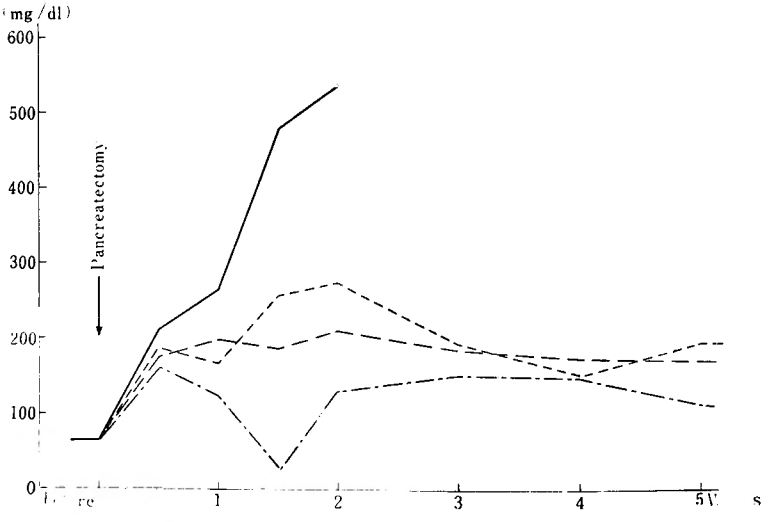
Total fatty acid in groups of simple administration of either insulin or estrogen and of simultaneous administration of these two showed slight increase with a little fluctuation after surgery (Fig. 5). In group without administration of drugs, it increased markedly compared with other groups.

**Fig. 5.** Change in Total Fatty Acid



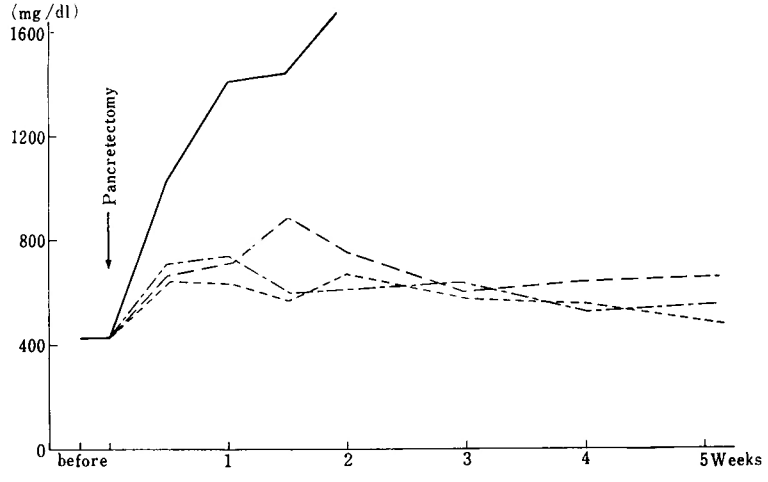

Neutral fat fluctuated in groups of simple administration of either insulin or estrogen and of simultaneous administration of these both, particularly in the third group after total pancreatectomy, and all of these showed the tendency of increase, being particularly marked in group without administration of drugs (Fig. 6).

**Fig. 6** Change in Neutral Fat



Total lipids increased moderately in groups of simple administration of either insulin or estrogen and of simultaneous administration of these two, and it increased remarkably in group without administration of drugs (Fig. 7).

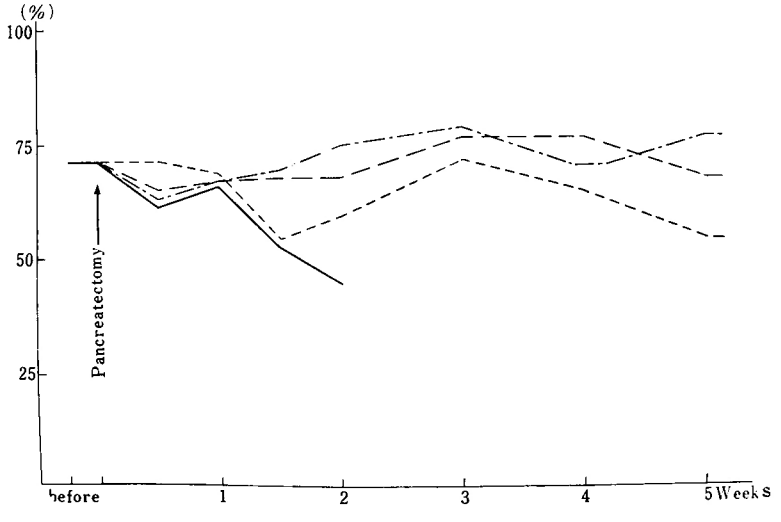
**Fig. 7.** Change in Total Lipids




Cholesterol ester ratio decreased approximately to 40 per cent in group without administration of drugs, whereas in groups of simple administration of either insulin or estrogen and of simultaneous administration of these both after total pancreatectomy, it remained within the physiological range (Fig. 8).

T.P./T.C. ratio was within the range of 0.73 to 1.21 at any period after surgery in groups of simple administraiton of either insulin or estrogen and of simultaneous administration of these both, and it was a little lower to be 0.55 in group without administration of drugs (Tab. 8, 9, 10 and 11).

**Fig. 8.** Change in Cholesterol Ester Ratio

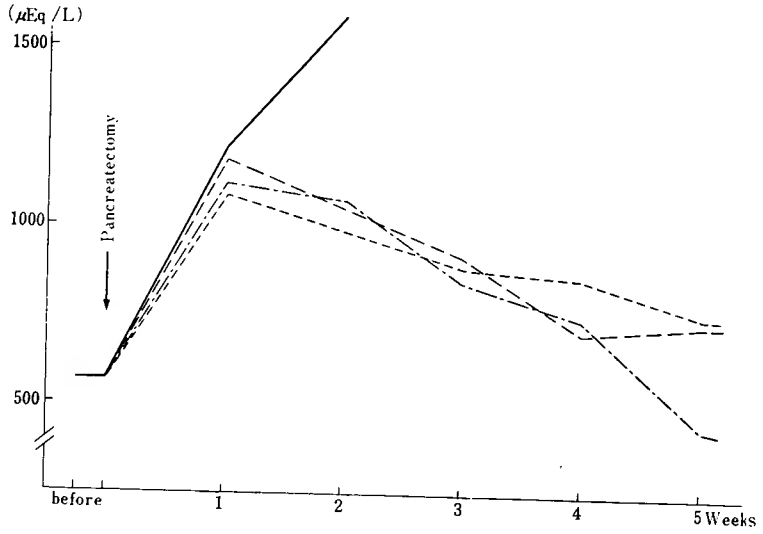


Non-esterified fatty acid (N.E.F.A.) rapidly increased after surgery in all groups, degree of which was slightly mild in groups of simple administration of either insulin or estrogen and of simultaneous administration of these two. Non-esterified fatty acid fluctuated in group with simple administration of estrogen resembling rather that of non-administration of drugs. In group without administration of drugs the value further increased on from 1st week to 2nd week, despite gradual decrease after the peak of 1st week in other 3 groups (Tab. 12 and Fig. 9).

**Table 12.** Change in Non-Estrified Fatty Acid. ($\mu$Eq/1)

| Group / Time after Surgery | Group without Administration of Drugs (5 dogs) | Group of Insulin Administrution (4 dogs) | Group of Estrogen Administration (7 dogs) | Group of Simultaneous Administration of Drugs (5 dogs) |
|---|---|---|---|---|
| before | 505±116 | 657±121 | 468±101 | 675± 98 |
| 1 Week | 1375±261 | 1097±361 | 1258±112 | 1140±215 |
| 2 Weeks | 1551±222 | 986±281 | 1053±123 | 1045±109 |
| 3 Weeks | — | 896±202 | 905±110 | 856±208 |
| 4 Weeks | — | 816±211 | 609±154 | 677±198 |
| 5 Weeks | — | 725±236 | 617±178 | 488±211 |

**Fig. 9.** Change in Non-Esteritied Fatty Acid




5. Liver Fat after Total Pancreatectomy

i. Liver Fat in Normal Dogs

Average value of liver fat in 17 normal dogs was determined to be 3.31 g/100 g of liver tissue (Tab. 13).

ii. Liver Fat in Totally Depancreatized Dogs

All the animals of group without administration of drugs died from 6 to 14 days after surgery (Tab. 14). Marked increase in liver fat was observed in each case at

**Table 13.** Amount of Liver Fat in Normal Dogs.

| Dog No. | Sex | Body Weight (kg) | Amount of Total Fatty Acid in Liver (g%) |
|---|---|---|---|
| 1 | ♂ | 6.0 | 2.36 |
| 2 | ♂ | 14.0 | 1.44 |
| 3 | ♀ | 9.5 | 2.56 |
| 4 | ♂ | 7.0 | 3.69 |
| 5 | ♀ | 6.0 | 2.93 |
| 6 | ♀ | 9.5 | 2.48 |
| 7 | ♀ | 11.0 | 4.73 |
| 8 | ♂ | 8.0 | 3.26 |
| 9 | ♀ | 10.5 | 3.28 |
| 10 | ♂ | 8.0 | 3.71 |
| 11 | ♂ | 8.0 | 2.78 |
| 12 | ♀ | 10.0 | 4.09 |
| 13 | ♂ | 12.0 | 3.29 |
| 14 | ♂ | 8.0 | 5.63 |
| 15 | ♀ | 9.5 | 4.09 |
| 16 | ♀ | 11.5 | 3.20 |
| 17 | ♂ | 7.5 | 2.98 |
| | Mean | | 3.31±0.58 |

autopsy, as in Table 14. Histlogically, liver tissue was filled with fatty drop-lets all over, revealing a finding of so-called "Totale Verfettung" (Photo 1).

In group of simple administration of insulin, animals survived for 28 to 46 days, and liver fat was 2.90 to 4.73 g/100 g of liver tissue remaining in normal range. Findings of fatty liver could not be observed histologically (Tab. 15 and Photo 2).

In group of simple administration of estrogen, marked increase in liver fat was observed in 4 cases out of 16, fatty liver developing in all animals (Tab. 16). These 4 dogs were those which received the administration of estrogen of a large dosis. Liver fat in 12 animals of the remainder was within normal range, and accumulation of fat could not be observed in the liver histologically (Photo 3).

In group of simultaneous administra-

**Table 14.** Liver Fat in Dogs Without Administration of Drugs.

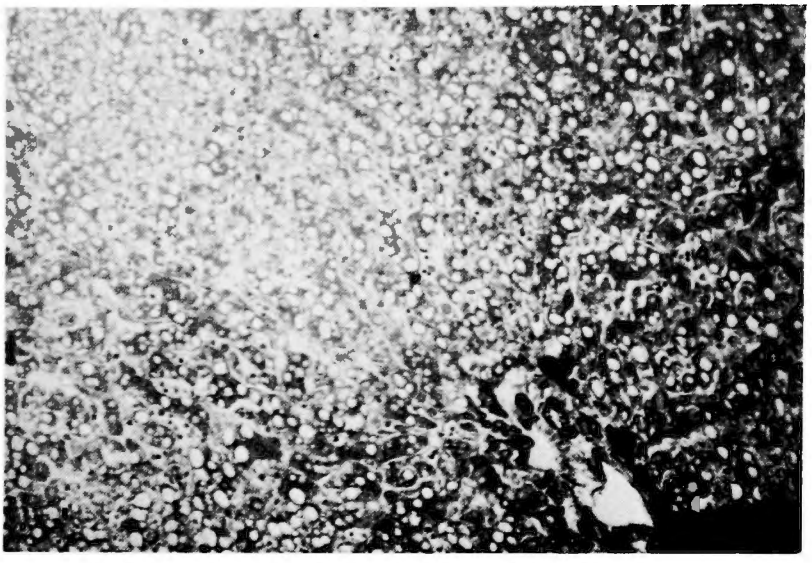
| Dog. No. | Sex | Body Weight before Surgery (kg) | Body Weight at Autopsy (kg) | Survival Time (day) | Liver Weight at Autopsy (g) | Liver Fat at Autopsy (g.%) | Cause of Death |
|---|---|---|---|---|---|---|---|
| 1 | ♀ | 8.0 | 5.5 | 14 | 355 | 14.10 | Fatty Liver |
| 2 | ♂ | 8.0 | 6.5 | 6 | 460 | 12.59 | Fatty Liver |
| 3 | ♀ | 12.5 | 8.5 | 12 | 689 | 13.80 | Fatty Liver |
| 4 | ♂ | 9.5 | 6.0 | 11 | 865 | 17.39 | Fatty Liver |
| 5 | ♀ | 7.5 | 5.5 | 9 | 535 | 9.31 | unknown |
| 6 | ♂ | 6.5 | 4.5 | 7 | 1010 | 16.81 | Fatty Liver |

tion of insulin and estrogen, fatty liver could be observed only in 1 case out of 11, with increase in liver fat, as shown in Table 17. Liver fat was in normal level in 10 animals of the remainder, and accumulation of fat could not be observed histologically (Photo 4).

6. Lipoprotein Lipase Activity after Total Pancreatectomy

As shown in Table 18 and Figure 10, activity of blood lipoprotein lipase 10 days after total pancreatectomy markedly decreased in group without administration of drugs, compared with normal dogs, which was slightly higher in group of simple administration of insulin. In groups of simple administration of estrogen and of simultaneous administration of insulin and estrogen, the value was almost near the normal level.

**Photo 1.** Liver of Dogs without Administration of Drugs.

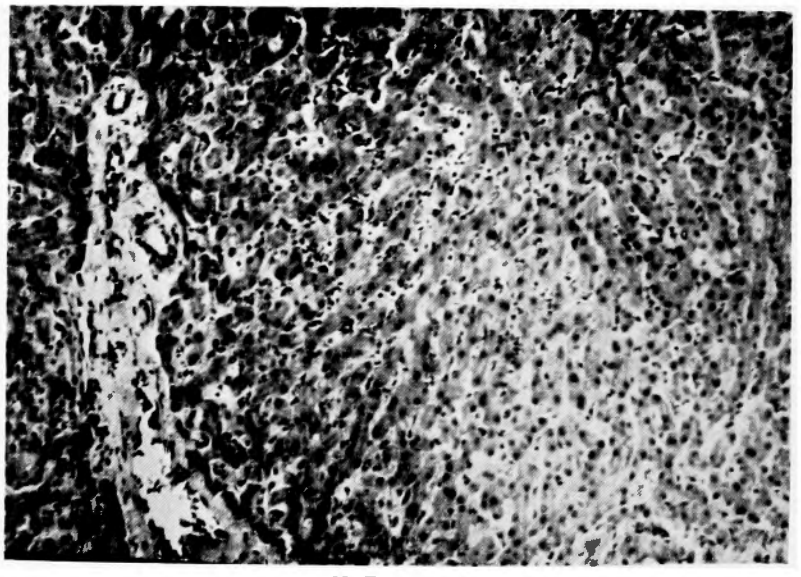


H. E. (×100)

**Table 15.** Liver Fat in Dogs of Insulin Administration.

| Dog No. | Sex | Body Weight before Surgery (kg) | Body Weight at Autopsy (kg) | Survival Time (day) | Liver Weight at Autopsy (g) | Liver Fat at Autopsy (g.%) | Dosis of Insulin (u./kg) | Cause of Death |
|---|---|---|---|---|---|---|---|---|
| 2 | ♂ | 9.5 | 5.0 | 46 | 255 | 2.90 | 1.5 | Death of Debility |
| 3 | ♀ | 8.5 | 6.0 | 40 | 275 | 3.63 | 1.5 | Death of Debility |
| 4 | ♂ | 9.0 | 6.5 | 31 | 365 | 4.73 | 1.5 | Death of Debility |
| 5 | ♀ | 10.5 | 7.5 | 28 | 285 | 3.04 | 2.0 | Death of Debility |

**Photo 2.** Liver of Dogs with Insulin Administration.

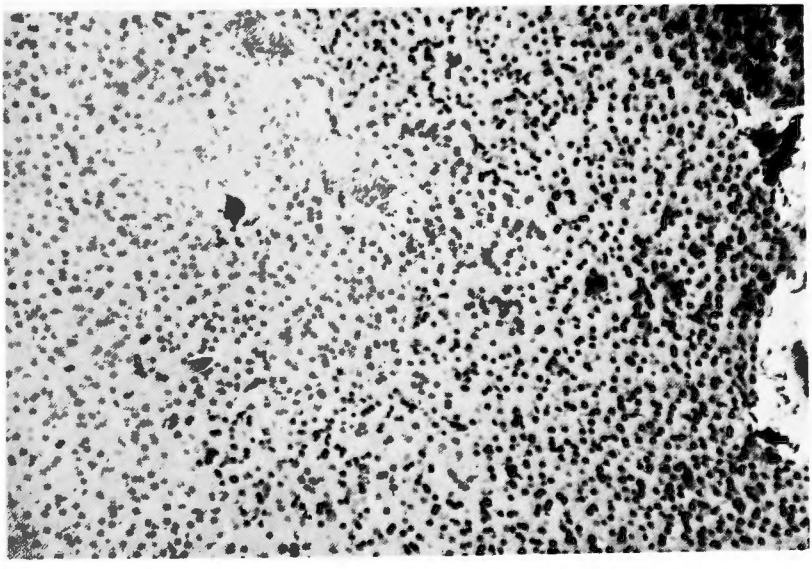


H. E. (×100)

**Table 16.** Liver Fat in Dogs of Estrogen Administration.

| Dog No. | Sex | Body Weght before Surgery (kg) | Body Weight at Autopsy (kg) | Survival Time (day) | Liver Weight at Autopsy (g) | Liver Fat at Autopsy (g.%) | Dosis of Estrogen (u./kg) | Cause of Death |
|---|---|---|---|---|---|---|---|---|
| 1 | 우 | 8.0 | 6.0 | 24 | 300 | 2.30 | 10,000 | Death of Debility |
| 2 | 우 | 10.0 | 8.0 | 7 | 680 | 16.00 | 20,000 | Fatty Liver |
| 3 | 우 | 11.0 | 7.5 | 26 | 365 | 3.13 | 10,000 | Death of Debility |
| 4 | 숫 | 9.5 | 8.5 | 4 | 400 | 12.60 | 20,000 | Fatty Liver |
| 5 | 숫 | 11.0 | 12.5 | 12 | 710 | 21.30 | 5,000 | Fatty Liver |
| 6 | 우 | 13.0 | 9.0 | 21 | 480 | 7.74 | 5,000 | Death of Debility |
| 7 | 우 | 7.5 | 4.0 | 23 | 200 | 2.39 | 5,000 | Death of Debility |
| 8 | 숫 | 14.0 | 11.0 | 18 | 350 | 3.17 | 1,000 | Death of Debility |
| 9 | 숫 | 9.5 | 6.5 | 107 | 260 | 2.75 | 1,000 | Death of Debility |
| 10 | 숫 | 15.0 | 10.5 | 30 | 265 | 3.78 | 1,000 | Death of Debility |
| 11 | 숫 | 14.5 | 6.0 | 27 | 350 | 8.51 | 1,000 | Death of Debility |
| 12 | 숫 | 10.5 | 6.0 | 35 | 385 | 4.12 | 1,000 | Death of Debility |
| 13 | 우 | 11.0 | 7.5 | 28 | 375 | 5.31 | 1,000 | Death of Debility |
| 14 | 우 | 12.5 | 9.5 | 29 | 285 | 13.87 | 1,000 | Fatty Liver |
| 15 | 우 | 9.0 | 6.0 | 45 | 315 | 6.14 | 1,000 | Death of Debility |
| 16 | 우 | 10.5 | 8.5 | 19 | 415 | 7.83 | 1,000 | Death of Debility |

**Photo 3.** Liver of Dogs of Estrogen Administration.

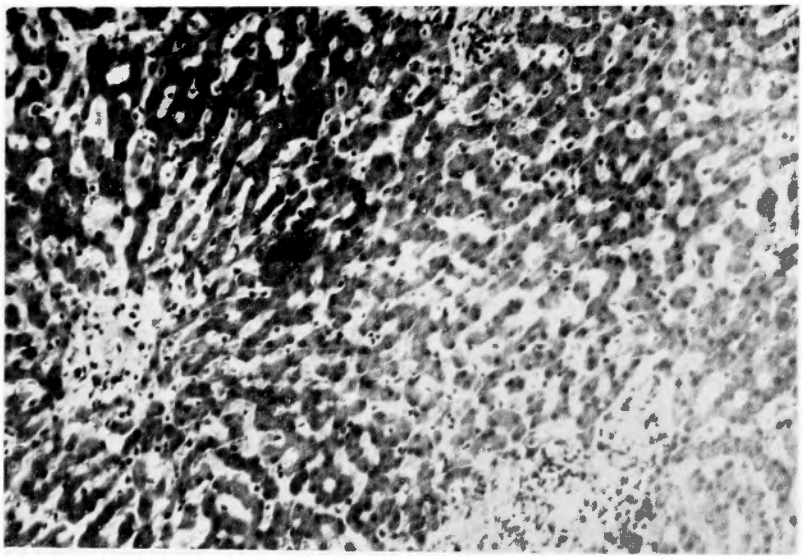


Sudan III (×100)

**Table 17.** Liver Fat in Dogs of Simultaneous Administration of Insulin and Estrogen.

| Dog No. | Sex | Body Weight before Surgery (kg) | Body Weight at Autopsy (kg) | Survival Time (day) | Liver Weight at Autopsy (g) | Liver Fat at Autopsy (g.%) | Dosis of Insulin (u./kg) | Dosis of Estrogen (u./kg) | Cause of Death |
|---|---|---|---|---|---|---|---|---|---|
| 1 | ♂ | 8.0 | 6.0 | 18 | 265 | 5.43 | 1.0 | 10,000 | Death of Debility |
| 2 | ♂ | 15.0 | 10.5 | 50 | 380 | 6.53 | 2.0 | 1,000 | Death of Debility |
| 3 | ♂ | 9.0 | 7.0 | 131 | 550 | 3.28 | 1.0 | 1,000 | Death of Debility |
| 4 | ♂ | 13.0 | 11.0 | 23 | 230 | 3.68 | 1.0 | 1,000 | Death of Debility |
| 5 | ♀ | 19.0 | 16.0 | 18 | 1070 | 17.25 | 0.5 | 5,000 | Fatty Liver |
| 6 | ♂ | 9.0 | 6.0 | 49 | 265 | 3.78 | 2.0 | 1,000 | Death of Debility |
| 7 | ♀ | 11.0 | 7.5 | 63 | 480 | 6.56 | 1.0 | 1,000 | Death of Debility |
| 8 | ♀ | 12.5 | 9.5 | 29 | 395 | 3.18 | 1.0 | 1,000 | Death of Debility |
| 9 | ♂ | 10.5 | 8.5 | 37 | 615 | 8.91 | 2.0 | 1,000 | Death of Debility |
| 10 | ♀ | 9.5 | 5.0 | 53 | 450 | 5.68 | 1.0 | 1,000 | Death of Debility |
| 11 | ♂ | 8.0 | 5.0 | 98 | 325 | 7.32 | 1.0 | 1,000 | Death of Debility |

**Photo 4.** Liver of Dogs of Simultaneous Administration of Insulin and Estrogen.



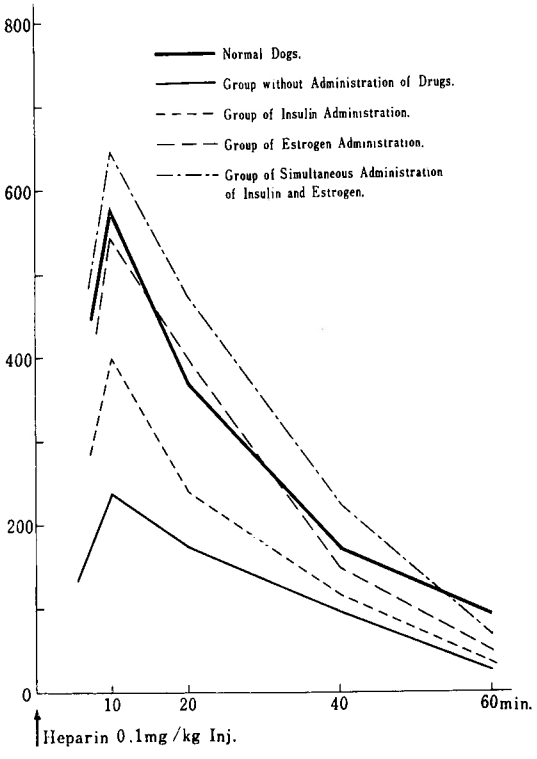
H. E. (×100)

**Table 18.** Change in Lipoprotein Lipase Activity

| Group | Dog No. | Time after Administration of Heparin | | | |
|---|---|---|---|---|---|
| | | 10 min. | 20 min. | 40 min. | 60 min. |
| Control Group | 21 | 707 | 538 | 216 | 142 |
| | 22 | 494 | 213 | 133 | 59 |
| | 24 | 622 | 407 | 151 | 78 |
| | 25 | 418 | 326 | 189 | 98 |
| Mean | | 560 | 371 | 172 | 94 |

| | | | | | |
|---|---|---|---|---|---|
| Group without Administration of Drugs | 19 | 301 | 205 | 129 | 54 |
| | 20 | 185 | 140 | 73 | 11 |
| | 21 | 219 | 186 | 85 | 23 |
| Mean | | 235 | 177 | 99 | 29 |
| Group of Insulin Administration | 15 | 387 | 258 | 107 | 28 |
| | 16 | 398 | 259 | 139 | 43 |
| | 17 | 421 | 225 | 84 | 12 |
| Mean | | 399 | 248 | 110 | 31 |
| Group of Estrogen Administration | 26 | 549 | 374 | 66 | 22 |
| | 27 | 720 | 645 | 355 | 118 |
| | 28 | 381 | 178 | 53 | 19 |
| Mean | | 550 | 399 | 158 | 53 |
| Group of Simultaneous Administration of Insulin and Estrogen | 19 | 699 | 492 | 198 | 53 |
| | 20 | 583 | 374 | 238 | 79 |
| | 21 | 702 | 586 | 264 | 102 |
| Mean | | 661 | 484 | 233 | 78 |

**Fig. 10.** Change in Lipoprotein Lipase Activity



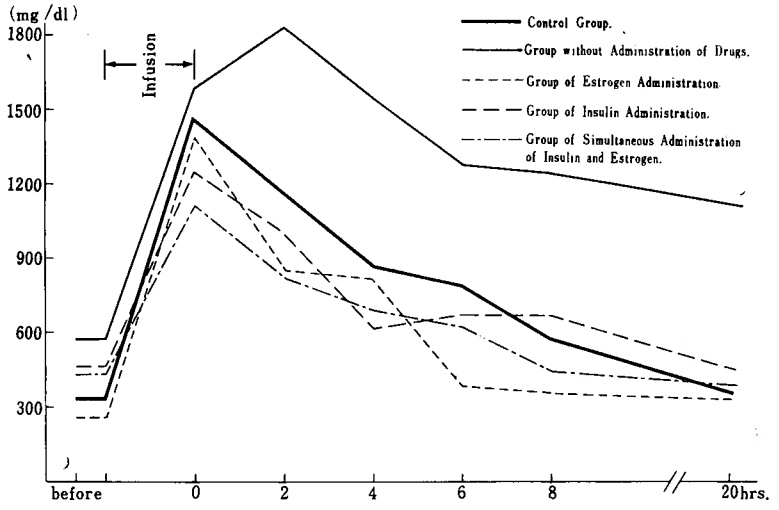
7. Change in Serum Lipids after Intravenous Administration of Fat after Total Pancreatectomy

Total fatty acid in blood was determined with the lapse of time after administration of fat emulsion. Total fatty acid remarkably increased immediately after administration of fat emulsion in groups of simple administration of either insulin or estrogen and of simultaneous administration of these two (Tab. 19 and Fig. 11), which then gradually decreased and returned to normal. This fluctuation closely resembles that of normal dogs after infusion of fat emulsion. In group without administration of drugs, different from other groups, total fatty acid in blood remarkably increased after infusion of fat emulsion, reaching its peak 2 hours after infusion with following gradual decrease, and still maintained considerably high level as late as 20 hours after infusion.

**Table 19.** Change in Total Fatty Acid in Serum after Intravenous Injection of Fat Emulsion.
(10% Fatgen of 20cc/kg Body Weight was infused in drip, spending 1～2 hours.) (mg/dl)

| Group | Dog No. | Days after Surgery | Before Administration | Time after Administration of Fat Emulsion | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 0 hr. | 2 hrs. | 4 hrs. | 6 hrs. | 8 hrs. | 20hrs. |
| Normal Group | 18 | — | 223 | 1284 | 986 | 806 | 425 | 484 | 297 |
| | 19 | — | 377 | 1428 | 1015 | 692 | 825 | 596 | 241 |
| | 20 | — | 348 | 1634 | 1277 | 1018 | 981 | 629 | 564 |
| Mean | | | 313 | 1449 | 1093 | 839 | 760 | 570 | 334 |
| Group without Administration of Drugs | 7 | 6 | 421 | 1781 | 2006 | 1836 | 1438 | 1528 | 1296 |
| | 8 | 9 | 693 | 1328 | 1805 | 1422 | 1393 | 1184 | 1007 |
| | 10 | 11 | 589 | 1684 | 1621 | 1331 | 989 | 973 | 984 |
| Mean | | | 567 | 1597 | 1811 | 1529 | 1273 | 1228 | 1096 |
| Group of Insulin Administration | 7 | 14 | 332 | 996 | 796 | 841 | 214 | 209 | 318 |
| | 9 | 13 | 273 | 1795 | 1221 | 1019 | 468 | 457 | 328 |
| | 12 | 16 | 241 | 1484 | 634 | 767 | 304 | 298 | 346 |
| Mean | | | 282 | 1425 | 884 | 876 | 329 | 325 | 330 |
| Group of Estrogen Administration | 19 | 12 | 428 | 1791 | 1368 | 803 | 874 | 992 | 581 |
| | 22 | 14 | 631 | 1116 | 784 | 432 | 598 | 365 | 421 |
| | 24 | 15 | 374 | 1234 | 1055 | 641 | 923 | 818 | 617 |
| | 25 | 18 | 468 | 917 | 692 | 548 | 455 | 687 | 399 |
| Mean | | | 475 | 1264 | 975 | 606 | 712 | 715 | 504 |
| Group of Simultaneous Administration of Drugs | 14 | 15 | 327 | 867 | 546 | 428 | 328 | 215 | 306 |
| | 15 | 17 | 431 | 1513 | 1138 | 887 | 789 | 298 | 321 |
| | 17 | 18 | 612 | 1044 | 674 | 659 | 777 | 682 | 515 |
| Mean | | | 458 | 1141 | 786 | 658 | 631 | 432 | 347 |

**Fig. 11.** Change in Total Fatty acid in Serum after Intravenous Injection of Fat Emulsion




## IV. DISCUSSION

Principal clinical picture after total pancreatectomy is characterized by diabetes mellitus, fatty liver and disturbance of digestion and absorption, and the operation is invariably lethal within 2 weeks when insulin is not administered. However, in the present experiment, marked prolongation of survival time could be observed to be more than 4 weeks in administration of estrogen. The rate of weight loss also showed considerably low value in animals with administration of estrogen to be 9.3 and 17.0 per cent, 1 and 2 weeks after surgery, respectively, whereas it was 18.3 and 30.1 per cent, 1 and 2 weeks after surgery, respectively, in animals without administration of drugs. Weight loss was further slight in animals with simultaneous administration of insulin and estrogen. Thus, it was observed that estrogen favorably influences on the general condition of totally depancreatized dogs. From this finding, the relationship between estrogen and carbohydrate metabolism first provided the problem. HOUSSAY[39)40)] observed that estrogen acts as a depressor of diabetes mellitus in partially depancreatized rats. HASEGAWA[41)], KURIMOTO[42)] and others also reported the beneficial effect of estrogen on diabetes. In the present experiment, however, influence of estrogen on blood sugar level in totally depancreatized dogs could not be observed at all. MIWA[43)], in our clinic, studied the fluctuation of blood sugar level in totally depancreatized dogs under the administration of estrogen of various dose, but he could not recognized effect of estrogen on decreasing blood sugar level. In this respect, it is presumed that favorable effect of estrogen in totally depancreatized dogs might not be attributable to immediate effect, at least, on carbohydrate metabolism. Why does estrogen influence favorably on general condition of totally depancreatized dogs ?

It has been pointed out since early days that there exists abnormality of blood lipids, particularly lipemia in the diabetics and experimental diabetes mellitus, and it is also widely accepted that arteriosclerosis, as a complication of diabetes mellitus, is due to

abnormality of fat metabolism including abnormality of blood lipids. From numerous studies of early days on blood lipids and estrogen, it has been presumed that estrogen might be possessed of certain influence on the abnormality of lipids in blood. OKEY and others reported in 1927 that serum cholesterol level fluctuates periodically corresponding to female sexual cycle[44]. ELILERT and others observed an increase in serum phospholipids after administration of estrogen in female of crimacterium[45][46]. BARR[47] reported that decrease in cholesterol level and increase in phospholipids could be observed following administration of estrogen in patients of myocardial infarction. OLIVER and others[48] also insisted that estrogen was effective in hypercholesterinemia accompanied by coronal disease. In addition, estrogen has been used for long period of time in the aim of decholesterilizer in patients of coronal disease and hypercholesterinemia by ROBINSON[49][50] and many other investigators[51][52][53][54].

On the other hand, MOSKOWITZ[55] recognized the effect of estrogen to reduce serum cholesterol level in rats with experimental hypercholesterinemia produced by ordinary diet rich in cholesterol. STAMLER and others[56] reported that estrogen has the effect of preventing Cockerele from atheromatous scleromatous sclerosis experimentally fed with diet rich in cholesterol and fat, which was based on the clinical observation that female diabetics are resistant to coronal sclerosis.

As obviously understood from the reports of so many investigators, anti-lipemic effect of estrogen has been generally admitted. In the present experiment also, lipemia was observed in animals without administration of drugs after total pancreatectomy. On the contrary, in animals with administration of estrogen, blood lipids showed the tendency of restoration to normal from 3 to 4 weeks after surgery, with exception of a few cases of fatty liver. When insulin was administered, the results were even more favorable. From these findings it is assumed that estrogen is effective directly or indirectly in normalization of fat metabolism, in other words, in normalization of lipoprotein picture.

Concerning non-esterified fatty acid in blood among lipids in blood, DOLE[33] discovered in 1956 the method of its determination credible to some extent. Following this discovery, it is being clarified gradually that non-esterified fatty acid plays an important role in the aspect of lipids transport and energy metabolism, although there remain many problems to be solved, including the relation to estrogen. In this point, non-esterified fatty acid level is higher in females and non-esterified fatty acid response to the administration of glucose and insulin is also more remarkable in females, according to the report of MOORHOUSE[57] on sexual difference in non-estrified fatty acid in blood in diabetics. However, SINKO and others[58] demonstrated that non-esterified fatty acid level was lower in females of 20 to 30 years of age from the observation of 275 cases of healthy men and women in the fasting state. He interpreted this finding to indicate that fatty acid is more readily isolated in relatively young men and reversed in females. KATO[59] also obtained the results that non-esterified fatty acid level was lower in cases with higher urinary estrogen level, though he could not clarify the significance of this finding. Non-esterified fatty acid in blood of totally depancreatized dogs in the present experiment was the highest in group without administration of drugs and it was a little lower in group of simple administration of estrogen. This tendency was intensely observed 2 weeks after

surgery. In group of simple administration of insulin and that of simultaneous administration of insulin and estrogen, non-esterified fatty acid level was in a high level, although a little higher in the latter 1 week after surgery. This difference was inverted 4 weeks after surgery, the level becoming a little higher in the former. From these findings, it can be justifiably said that estrogen is possessed of an effect to decrease non-esterified fatty acid in blood of totally depancreatized dogs.

On the other hand, there has been numerous investigations on fatty liver after total pancreatectomy, with special reference to insulin and anti-fatty liver substance, and it is accepted that administration of insulin of suitable dose or its simultaneous administration with anti-fatty liver substance can prevent development of fatty liver[24)25)]. In the present experiment also, development of fatty liver could be hardly observed in group of simple administration of insulin. In animals with administration of estrogen after total pancreatectomy, occurrence of fatty liver was observed in 3 cases out of 16, and fatty liver could be hardly recognized in animals with administration of estrogen of 1,000 to 2,000 units per kg body weight. These 3 animals with post-pancreatectomic fatty liver were treated with large dose of estrogen and fatty liver developed in the early period after surgery leading the animals to death. In this respect, it is assumed that dosis of estrogen administration should be further investigated, as one reflects upon the observation of MACBRYDS[60)] that estrogen administration of large dose resulted in fat infiltration in the liver of dogs. Anyway, it is interpreted that the results of the present experiment demonstrate anti-fatty liver effect of estrogen in totally depancreatized dogs. Concerning the influence of estrogen on liver fat, GYÖRGY and others[61)] reported in 1949 that estrogen is effective for fat infiltration in the liver of animals fed with low protein and high fat diet. BLOHM[62)] observed marked decrease in lipids of the serum, lung, liver and aorta in rats after 3 months' administration of MER-29, a derivative of estrogen. However, there are reports that administration of estrogen caused fat infiltration in the liver, and the problem cannot be accepted thoroughly clarified. Anyhow, it is presumed that estrogen exerts anti-fatty liver effect, participating in phospholipids metabolism, as is suggested by the effect of phospholipids on fatty liver after total pancreatectomy and by the assertion of TAUROG[63)] that estrogen improves synthesis of phospholipids in the liver.

In 1943, HAHN[64)] discovered that heparin has an effect of purifying alimentary lipemia in dogs as injected intravenously. Since this discovery, interest of investigators was attracted to a certain substance having an effect of clearing lipemia after intravenous administration of heparin, and many reports appeared on the entity and mechanism of action of this substance. According to these reports, this substance is thought to be a new enzyme and called clearing factor or lipoprotein lipase. Owing to the recent advance in analysis method of lipids, a new concept became to be introduced in the mode of existence of blood lipids, and it is considered that the clearing factor, i. e. lipoprotein lipase has close association to normalization of lipemia or lipoprotein picture. STORK and others[65)], in 1957, observed that activity of lipoprotein lipase was decreased in diabetics compared with normal persons, which was particularly serious in cases accompanied by arteriosclerosis. From the determination of activity of lipoprotein lipase in blood after intravenous injection of heparin in alloxan-rats, MENG and GOLDFARB[66)] also reported

that the activity was remarkably decreased compared with normal rats, but this decrease was fairly improved by the administration of insulin and completely recovered by oral administration of dried pancreas. ARISAKA[67] determined production of clearing factor of various organ tissue, and he observed that the production of this factor was outstandingly high in the pancreatic tissue. Thus, he presumed that the pancreas might be closely associated with the production of clearing factor. Lately, in 6 cases of cystic fibrosis of the pancreas, SLACK and others[68] determined activity of blood lipoprotein lipase after intravenous injection of heparin and they recognized marked decrease in all cases. All these reports are accepted to indicate that there exists some interrelation between the pancreas and blood lipoprotein lipase. According to the report of OVERBEEK[69], activity of lipoprotein lipase actually decreased in totally depancreatized dogs within a few days after surgery, which increased to normal level by the administration of insulin 2 weeks after surgery. Decrease in activity of lipoprotein lipase was marked in animals without administration of drugs in the present experiment, while the decrease was only in a slightest degree in animals with administration of insulin.

In animals with estrogen administration, the activity of this enzyme was maintained in a similar level as in normal ones. In animals with administration of insulin and estrogen, the activity rather showed a tendency of an increase compared with normal animals. This finding is interpreted to demonstrate the influence of estrogen on activity of lipoprotein lipase in totally depancreatized dogs obviously, closely correlating with the results of above mentioned blood lipids.

There have been many attempts to clarify the mechanism of fat transport by observing swiftness of disappearance of fat from blood after intravenous injection of fat emulsion. RONY[70] reported in 1931 that disappearance of injected fat emulsion was retarded in totally depancreatized dogs and reduced fat tolerance could be improved to normal by administration of insulin, which was also demonstrated similarly by WADDEL and others[71]. KESSLER[72] reported that when fat emulsion is infused to normal dogs, there emigrates fat decomposing enzyme in blood having a similar character as lipoprotein lipase, and he maintained that the activity of this enzyme is proportionate to the rate of neutral fat transport from blood. In the present experiment, influence of insulin and estrogen on activity of this enzyme was studied following infusion of fat emulsion, and a marked increase in fat of blood immediately after the infusion in all groups, the level of blood fat restoring to that before the infusion 20 hours later in groups of simple administration of either insulin or estrogen and of simultaneous administration of these both, whereas it showing yet a high value 20 hours after the infusion in group without administration of drugs. This finding is interpreted to suggest that transport of infused fat is disturbed in group without administration of drugs. The fact that transport of neutral fat was not disturbed even in group of simple administration of estrogen demonstrates that estrogen plays an important role in transportation of fat, providing interesting problems together with the finding of well maintained activity of lipoprotein lipase. In recent years, ANDO and others[73] reported that estrogen is effective in 'shifting action' of fat, decreasing C/P ratio and promoting conversion of cholesterol into bile acid in the liver of rats. This observation is accepted to support the findings of the present experiment, also.

## V. SUMMARY

Studies were carried out on fat metabolism in totally depancreatized dogs under administration of insulin and estrogen.

1. Weight loss after total pancreatectomy was mild in group of simple administration of estrogen compared with animals without administration of drugs, it being more slight when treated with insulin.

2. Blood sugar level in the fasting state after total pancreatectomy was not influenced by the administration of estrogen.

3. Serum lipids after total pancreatectomy showed moderate increase in groups of simple administration of either insulin or estrogen and that of simultaneous administration of these two, with no particular difference from each other, while remarkable lipemia was observed in group without administration of drugs.

4. Although fatty liver almost invariably developed after total pancreatectomy in group without administration of drugs and the animals died within 2 weeks, it was observed only in 3 cases out of 16 in group of simple administration of estrogen, survival time also being prolonged over 4 weeks.

5. Activity of lipoprotein lipase was fairly maintained in a favorable level by the administration of estrogen, and simultaneous administration of insulin with it improved the value to be near the normal one.

6. When fat emulsion was intraveously infused, amount of fat in blood returned to normal 20 hours after the infusion in all groups except that without administration of drugs, in which the amount of fat in blood showed a higher level 20 hours after the infusion, yet.

From all the results above mentioned, it is assumed that administration of estrogen improves general condition after total pancreatectomy. This effect of estrogen is considered to consist in the improvement of fat metabolism after total pancreatectomy, and more favorable effect was obtained by simultaneous administration of insulin which normalizes carbohydrate metabolism.

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(* in Japanese)

## 和 文 抄 録

# 膵全剔後の脂質代謝に及ぼすエストロゲンの影響

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膵全剔犬に各種単位のインシュリン及びエストロゲンを，或はエストロゲン単独を注射し，インシュリン単独投与の犬及び薬剤無投与の犬と比較してその病態生理を脂質代謝の面から種々検討し，次の結果を得た．

1. 膵全剔後の体重減少は薬剤無投与群に比しエストロゲン単独投与群では，程度が軽く，インシュリンとの併用は更に良好な成績を示した．

2. 膵全剔後の空腹時血糖値にはエストロゲン投与による特別の影響は認められなかつた．

3. 膵全剔後の血清脂質は，エストロゲン単独投与群，インシュリン単独投与群，併用投与群の何れも中等度の上昇を示すが，3者には有意の差は認められず，薬剤無投与群では著明な高脂血症を示した．

4. 膵全剔後，薬剤無投与群では殆どが脂肪肝を呈するが，エストロゲン単独投与群では，17頭中僅か3頭に脂肪肝が認められ，無投与群では2週以内に死亡するに比し，エストロゲンの投与は生存日数を4週以上に延長せしめ得た．

5. 膵全剔犬の血中 Lipoprotein lipase 活性はエストロゲン投与により可成り良く維持され，インシュリンの併用は更に正常に近い値を示した．

6. 経静脈的に脂肪を点滴注入しても，薬剤無投与群以外の3群では注入後20時間には血中脂肪量は注入前の値に復した．薬剤無投与群では注入後20時間においても尚高値を示した．

以上の結果より膵全剔後エストロゲンの投与は全身状態を改善せしめ得るもので，このエストロゲンの作用は術後の脂質代謝に好影響をもたらすことによるものであり，糖代謝を正常化せしめるインシュリンとの併用により更に良好な結果が得られた．